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Risk Factors for Antibiotic-Resistant *Escherichia coli* Isolated from Hospitalized Patients with Urinary Tract Infections: a Prospective Study

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From November 1998 to February 1999 we prospectively evaluated the prevalence of resistance to penicillins, cephalosporins, carbapenem, quinolones, aminoglycosides, and trimethoprim-sulfamethoxazole (SXT) in 320 *Escherichia coli* isolates isolated from hospitalized patients with acute urinary tract infections (UTIs). We also studied for these strains risk factors for resistance to amoxicillin-clavulanic acid (AMC), fluoroquinolones (FQs), and SXT. Resistance rates were consistent with those from major recent studies reported in the literature. Multivariate analyses selected the following factors as being significantly associated with *E. coli* resistance: (i) for resistance to AMC, prior (1 year) UTI (odds ratio [OR] = 2.71, $P = 0.006$), prior (1 year) urinary catheter (OR = 2.98, $P = 0.0025$), and prior (6 months) antibiotic exposure (OR = 2.68, $P = 0.005$); (ii) for resistance to FQs male sex (OR = 3.87, $P = 0.03$), with a trend toward significance for age >65 years (OR = 7.67, $P = 0.06$) and prior (1 year) UTI (OR = 2.98, $P = 0.07$); and (iii) for resistance to SXT, male sex (OR = 1.91, $P = 0.046$), hospitalization in an intermediate-term-care unit (OR = 2.18, $P = 0.008$), and prior (1 year) UTI (OR = 2.03, $P = 0.03$). Ours results suggest that prior UTI is a common risk factor for resistance to the different antibiotics tested. Although few studies on risk factors for *E. coli* resistance to antibiotics have been published, careful interpretation of their findings, taking into consideration the population, infection site, and period studied, should contribute to the formulation of a better strategy that can be used to overcome antibiotic resistance.

Escherichia coli, the most common member of the family *Enterobacteriaceae* implicated in human infectious diseases, has not been spared acquisition of antibiotic resistance, a complex therapeutic problem (7, 15, 38). The evolution of this microorganism's antibiotic resistance patterns identified from clinical isolates has been reported in many studies on amoxicillin (AMZ), amoxicillin-clavulanic acid (AMC), fluoroquinolones (FQs), and trimethoprim-sulfamethoxazole (SXT). Also, the intimate mechanisms of *E. coli* antibiotic resistance have been studied and explained in numerous publications (23, 24, 26, 35, 39). Unfortunately, few analyses of the demographic, epidemiological, and clinical data for patients with *E. coli* infection for determination of risk factors for resistance to antimicrobial agents have been reported (1, 10, 13, 17, 27, 31).

To evaluate the prevalence of resistance to a panel of antibiotics, including penicillins, cephalosporins, carbapenem, quinolones, aminoglycosides, and SXT, of *E. coli* strains isolated from hospitalized patients with acute urinary tract infections (UTIs) and to identify the risk factors for *E. coli* resistance to AMC, FQs, and SXT, which are routinely used to treat these infections, we conducted a prospective study in our hospital over a 3-month period. We discuss our observations, taking into consideration the most recent major studies on *E. coli* resistance rates in Europe and North America and, when available, their analyses of risk factors for antibiotic resistance.

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MATERIALS AND METHODS

Population studied. University Hospital of Nîmes, Nîmes, which is in southern France, has 1,588 beds, including 824 acute-care (AC) beds, corresponding to the units dealing with patients with acute diseases: internal medicine; hemato-oncology; surgery; obstetrics-gynecology; and neonatal, pediatric, and intensive care units. The hospital has 281 intermediate-term-care (IC) beds, corresponding to the units dealing with patients who are in the convalescent phase or who require physical therapy, and 483 long-term-care (LC) beds, corresponding to the units dealing with patients with a chronic pathology necessitating long-term hospitalization (>1 month). Each year approximately 40,000 patients are admitted to the hospital. All hospitalized patients who had a documented *E. coli* UTI, according to the definitions of Rubin et al. (36) for adults and Rushton (37) for children, were prospectively enrolled between 15 November 1998 and 15 February 1999. For each patient, data were prospectively collected from an interview with the patient or the patient's family, medical records, and an interview with the patient's general practitioner when it was necessary. Patients from whom *E. coli* was isolated at least 48 h after admission were considered to have a nosocomial infection; all other infections were considered to be community acquired (18). The risk factors for resistance analyzed for each antibiotic, AMC, FQs, and SXT, were as follows: age; sex; unit of hospitalization (AC, IC, or LC unit); presence of urinary catheter; prior UTI, urinary catheter, or hospitalization during the previous year; and antibiotic exposure during the preceding 6 months, including antibiotics received as an outpatient.

Microbiological studies. Susceptibility testing was performed by the disk diffusion method with Mueller-Hinton medium (Sanofi Diagnostics Pasteur, Marne-la-Coquette, France). The results were analyzed according to the recommendations of the Antibiogram Committee of the French Society for Microbiology (8). The antibiotics tested were AMC, ticarcillin, ticarcillin-clavulanic acid, piperacillin, piperacillin-tazobactam, cefamandole, cefazolin, cefotaxime, ceftazidime, cefepime, imipenem, pipemidic acid, FQs (including norfloxacin, pefloxacin, ofloxacin, and ciprofloxacin), gentamicin, amikacin, and SXT. Isolates

TABLE 1. Rates of resistance to different antibiotics tested against 320 *E. coli* strains isolated from urinary tract infections[a]

Strain	Rate (%) of resistance to:															
	AMZ	AMC	TIC	TIM	PIP	TZP	CFZ	CTX	CAZ	FEP	IPM	PPA	FQs	GEN	AMK	SXT
S	51.9	79.7	53.1	93.1	59.4	97.5	91.2	99.1	99.4	99.7	100	87.1	94.7	97.2	98.8	73
R	46.2	5.6	46	1.3	19.7	0	2.5	0.3	0.3	0	0	9.1	5	1.9	0.6	23.5
I	1.9	14.7	0.9	5.6	20.9	2.5	6.3	0.6	0.3	0.3	0	3.8	0.3	0.9	0.6	3.4

[a] Abbreviations: AMZ, amoxicillin; AMC, amoxicillin-clavulanic acid; TIC, ticarcillin; TIM, ticarcillin-clavulanic acid; PIP, piperacilline; TZP, piperacillin-tazobactam; CFZ, cefazolin; CTX, cefotaxime; CAZ, ceftazidime; FEP, cefepime; IPM, imipenem; PPA, pipemidic acid; GEN, gentamicin; AMK, amikacin; S, susceptible strains; R, resistant strains; I, intermediate strains. The FQs comprised norfloxacin, pefloxacin, ofloxacin, and ciprofloxacin.

from the same patients with the same resistance pattern were excluded. Our definition of an FQ-resistant *E. coli* isolate was a strain resistant to at least one of the following FQs: norfloxacin, pefloxacin, ofloxacin, or ciprofloxacin.

Statistical analyses. Statistical analyses were performed with SAS software (version 6.08, 1987; SAS Institute Inc., Cary, N.C.). The influence of qualitative variables on *E. coli* resistance to the different antibiotics was assessed with crude odds ratios (ORs) calculated by the Mantel-Haenszel method and tested versus 0 by using Mantel-Haenszel χ^2 test. The 95% confidence intervals (CIs) are reported. Quantitative variables were compared between two groups (resistant versus susceptible) by Student's *t* test. An unconditional logistic regression analysis was performed, with variables significant at a *P* value of ≤0.20, as assessed by univariate analysis, to control for all the confounding factors. Variables were introduced into the multivariate analysis in a stepwise manner to construct the final model. A *P* value of ≤0.05 was considered significant.

RESULTS

During the study period, a total of 320 nonduplicate consecutive and clinically significant *E. coli* isolates were collected from 246 women (76.9%) and 74 men (23.1%), whose mean age was 61.7 years (range, 0 to 96 years). Two hundred forty-two (75.6%) of them were hospitalized in AC units, 49 (15.3%) were hospitalized in IC units, and 29 (9.1%) were hospitalized in LC units.

The rates of resistance to different antibiotics tested are reported in Table 1. Among the antibiotics tested in our study, the highest rates of resistance (for intermediate plus resistant strains) were found for AMZ (48.1%), ticarcillin (46.9%), piperacillin (40.6%), SXT (26.9%), AMC (20.3%), pipemidic acid (12.9%), and FQs (5.3%). Rates of resistance to aminoglycosides were below 3%, with amikacin having better activity (rate of resistance to amikacin, 1.2%). Broad-spectrum cephalosporins remained highly active, with the rate of resistance to these drugs being <1%. Imipenem was always active.

Eighty patients had received antibiotic treatment during the preceding 6 months. Two patients received two antibiotics during this period. The prescriptions corresponded to AMC in 23 patients, AMZ in 19 patients, other β-lactams in 9 patients, FQs in 7 patients, SXT in 3 patients, and other classes of antibiotics in 21 patients.

According to univariate analysis, *E. coli* resistance to AMC was significantly higher in patients with prior hospitalization ($P = 0.009$), prior UTI ($P < 0.001$), prior urinary catheter ($P < 0.001$), and prior antibiotic exposure ($P < 0.001$) and patients hospitalized in an LC unit ($P < 0.04$) (Table 2). Prior exposure to AMC had not significantly influenced *E. coli* resistance to AMC. Multivariate analysis retained prior UTI ($P = 0.006$), prior urinary catheter ($P = 0.003$), and prior antibiotic exposure ($P = 0.005$) as being significantly associated with AMC resistance (Table 3).

For FQs, univariate analysis indicated that age >65 years ($P = 0.003$) and prior UTI ($P = 0.034$) were significantly associated with *E. coli* resistance. There was a trend toward significance for men ($P = 0.07$), prior hospitalization ($P = 0.09$), and hospitalization in an IC unit ($P = 0.08$) (Table 4). Prior exposure to FQs had not significantly influenced *E. coli* resistance to FQs. By multivariate analysis, *E. coli* strains isolated from men were significantly more resistant than those isolated from women ($P = 0.003$), while the relationship to *E. coli* resistance of age >65 years ($P = 0.06$) and prior UTI ($P = 0.07$) (Table 5) approached significance.

For SXT, univariate analysis showed that *E. coli* resistance was significantly higher in patients who were hospitalized in IC units ($P = 0.03$) and who had previously had a UTI ($P = 0.008$). There was a trend toward significance for prior hospitalization ($P = 0.09$) (Table 6). Prior exposure to SXT had not significantly influenced *E. coli* resistance to SXT. Three risk factors significantly associated with SXT-resistant *E. coli* were retained by multivariate analysis: men ($P = 0.046$), hospitalization in an IC unit ($P = 0.008$), and prior UTI ($P = 0.03$) (Table 7).

DISCUSSION

The comparison of rates of *E. coli* resistance to amoxicillin, AMC, FQs, and SXT determined in different studies performed in Europe and North America since 1990 prompts several remarks. AMZ resistance rates were frequently >30% and tend to be rising. In our study, this rate was 48.1%. In the United States, Gupta et al. (21) reported that the rate of resistance to aminopenicillin rose from 26 to 34% during the 5-year period from 1992 to 1996 in women with acute uncomplicated cystitis seen at outpatient clinics or emergency departments of a managed care center. In a second study concerning women with the same symptoms and consulting a sexually transmitted disease clinic, the same group compared rates of resistance to AMZ in 1989 to 1991 and 1995 to 1997, when the rates were 29 and 35%, respectively (20). Similar trends were observed in other countries. In the United Kingdom, during a 22-year period (1971 to 1992) the rate of resistance of *E. coli* strains isolated from patients with UTIs rose from 11.8 to 43.3% for outpatients and from 33.9 to 46.5% for inpatients (19). In The Netherlands, this rate increased from 24.7% in 1982 to 34% in 1992 for *E. coli* strains isolated from all outpatient specimens (4), and in France, this rate increased from 32% in 1982 to 45% in 1993 for all *E. coli* strains isolated from hospitalized patients (11) and from 26 to 47% for strains isolated from outpatients with UTIs (10).

We found an AMC resistance rate of 20.3%, consistent with two studies (1, 22) which reported AMC resistance rates of 19

TABLE 2. Factors associated with *E. coli* resistance to AMC as assessed by univariate analysis

Risk factor	No. (%) of patients[a]		OR (95% CI)	*P* value
	I-R	S value		
Age>65 yr	65	255		
No	22 (33.9)	105 (41.2)	1	
Yes	43 (66.1)	150 (58.8)	1.37 (0.77–2.42)	0.29
Sex	65	255		
Female	49 (75.4)	197 (77.3)	1	
Male	16 (24.6)	58 (22.7)	1.11 (0.59–2.10)	0.75
Unit of hospitalization	65	255		
AC	43 (66.1)	199 (78.0)	1	
IC	12 (18.5)	37 (14.5)	1.50 (0.73–3.11)	0.28
LC	10 (15.4)	19 (7.5)	2.44 (1.08–5.50)	0.04
Nosocomial acquisition	65	255		
No	48 (73.8)	161 (63.1)	1	
Yes	17 (26.2)	94 (36.9)	1.65 (0.89–3.02)	0.11
Urinary catheter	64	255		
No	47 (73.4)	195 (76.5)	1	
Yes	17 (26.6)	60 (23.5)	1.18 (0.63–2.20)	0.62
Prior (1 yr) hospitalization	60	208		
No	20 (33.3)	109 (52.4)	1	
Yes	40 (66.7)	99 (47.6)	2.20 (1.21–3.99)	0.009
Prior (1 yr) UTI	60	208		
No	26 (43.3)	164 (78.8)	1	
Yes	34 (56.7)	44 (21.2)	4.87 (2.72–8.73)	0.001
Prior (1 yr) urinary catheter	62	208		
No	33 (53.2)	174 (83.7)	1	
Yes	29 (46.8)	34 (16.3)	4.50 (2.48–8.14)	0.001
Prior (6 mo) antibiotic exposure	65	255		
No	32 (49.2)	208 (81.6)	1	
Yes	33 (50.8)	47 (18.4)	4.57 (2.62–7.94)	0.001

[a] I-R, intermediate and resistant strains; S, susceptible strains.

and 18%, respectively, in 1993 for outpatient populations. These rates are lower than others published since 1990, which were frequently about 25 to 30% (2, 9, 27, 29, 33, 34) and which could reach 40% or more (22, 25, 41). These data were collected for hospitalized patients. Conversely, two recent studies obtained rates of <15%. One of them concerned community-acquired UTIs in adults (16); the other concerned UTIs in female students (12). However, in the latter study, strains with intermediate resistance to AMC were not included in the percentage of resistant bacteria.

TABLE 3. Multivariate analysis of independent risk factors for *E. coli* resistance to AMC

Risk factor	OR (95% CI)	*P* value
Unit of hospitalization		
AC	1	
IC	1.60 (0.60–4.27)	0.36
LC	2.25 (0.86–5.86)	0.10
Prior (1 yr) UTI		
No	1	
Yes	2.71 (1.34–5.47)	0.006
Prior (1 yr) urinary catheter		
No	1	
Yes	2.98 (1.47–6.04)	0.003
Prior (6 mo) antibiotic exposure		
No	1	
Yes	2.68 (1.35–5.31)	0.005

Rates of resistance to SXT have progressively increased over the past several years, exceeding 15% in almost all recent studies conducted in different countries of Europe and North America (1, 4, 12, 16, 19, 20, 21, 27, 34). Several investigators reported rates between 30 and 40% (1, 10, 25, 40, 41). With a resistance rate of 26.9%, our findings are consistent with the rates reported in the literature.

In our study, the overall rate of resistance to FQs (norfloxacin, ofloxacin, pefloxacin, and ciprofloxacin) was 5.3%. Reported studies, which primarily considered ciprofloxacin and then norfloxacin, showed that trends toward *E. coli* resistance to this class of antibiotic have steadily increased since its introduction (14, 17, 31, 32). The resistance rates were frequently between 3 and 10%. However, rates differed widely from one study to another. For example, Gupta et al. (20, 21) investigated UTIs in young women who were outpatients and found resistance rates of 0 to 0.2%, whereas others investigators

TABLE 4. Factors associated with *E. coli* resistance to FQs as assessed by univariate analysis

Risk factor	No. (%) of patients[a]		OR (95% CI)	*P* value
	I-R	S		
Age >65 yr	17	303		
No	1 (5.9)	126 (41.6)	1	
Yes	16 (94.1)	177 (58.4)	11.39 (2.23–58.20)	0.003
Sex	17	303		
Female	10 (58.8)	236 (77.9)	1	
Male	7 (41.2)	67 (22.1)	2.46 (0.93–6.54)	0.07
Unit of hospitalization	17	303		
AC	10 (58.8)	232 (76.6)	1	
IC	2 (11.8)	27 (8.9)	2.63 (0.89–7.81)	0.08
LC	5 (29.4)	44 (14.5)	1.72 (0.36–8.14)	0.50
Nosocomial acquisition	17	303		
No	12 (70.6)	197 (65.0)	1	
Yes	5 (29.4)	106 (35)	1.29 (0.44–3.76)	0.64
Urinary catheter	17	302		
No	13 (76.5)	229 (75.8)	1	
Yes	4 (23.5)	73 (24.2)	0.97 (0.30–3.06)	0.95
Prior (1 yr) hospitalization	15	253		
No	4 (26.7)	125 (49.4)	1	
Yes	11 (73.3)	128 (50.6)	2.69 (0.87–8.34)	0.09
Prior (1 yr) UTI	15	253		
No	7 (46.7)	183 (72.3)	1	
Yes	8 (53.3)	70 (27.7)	2.99 (1.09–8.21)	0.034
Prior (1 yr) urinary catheter	15	255		
No	12 (80)	195 (76.5)	1	
Yes	3 (20)	60 (23.5)	0.81 (0.22–2.98)	0.76
Prior (6 mo) antibiotic exposure	17	303		
No	12 (70.6)	228 (75.2)	1	
Yes	5 (29.4)	75 (24.8)	1.27 (0.43–3.71)	0.67

[a] I-R, intermediate and resistant strains; S, susceptible strains.

found that resistance rates for *E. coli* strains isolated from urine were as high as 20.6% and that 20% of strains from hospitalized patients were ciprofloxacin resistant (14, 19). In addition, investigators have found that 29% of strains from nursing home patients were norfloxacin resistant (40).

The regional variations of *E. coli* resistance to antibiotics could be explained in part by different local antibiotic practices. The emergence of antibiotic-resistant strains is a major therapeutic problem that is multifactorial and that could be explained by several nonexhaustive hypotheses. The influence of excessive and/or inappropriate antibiotic use, particularly of broad-spectrum agents prescribed empirically, has been demonstrated. Reducing the number of prescriptions of a particular antibiotic can lead to a decrease in resistance rates (17, 28). Conversely, Ena et al. (14) observed an increase in the rate of ciprofloxacin resistance among *E. coli* strains from 3 to 20%; this was observed concomitantly with a tripling in the rate of consumption of FQs during the same period. Transmission of resistant isolates between people and/or by consumption of food from animals that had received antibiotics (3, 5) and greater mobility of individuals worldwide have also contributed to the extension of antibiotic resistance.

Because of the continuous evolution of antibiotic resistance, regular monitoring of this phenomenon appears to be necessary to improve guidelines for empirical antibiotic therapy, which must consider the most probable microorganisms, their susceptibilities according to the characteristics of the population concerned, without forgetting side effects, and ecological and economic consequences. From the characteristics of the

TABLE 5. Multivariate analysis of independent risk factors for *E. coli* resistance to FQs

Risk factor	OR (95% CI)	*P* value
Age >65 yr		
No	1	
Yes	7.67 (0.96–61.52)	0.06
Sex		
Female	1	
Male	3.87 (1.20–12.49)	0.03
Prior (1 yr) UTI		
No	1	
Yes	2.98 (0.92–9.64)	0.07

TABLE 6. Factors associated with *E. coli* resistance to SXT as assessed by univariate analysis

Risk factor	No. (%) of patients[a]		OR (95% CI)	*P* value
	I-R	S		
Age >65 yr	87	229		
No	33 (37.9)	90 (39.3)	1	
Yes	54 (62.1)	139 (60.7)	1.11 (0.67–1.84)	0.70
Sex	87	233		
Female	62 (71.3)	184 (79)	1	
Male	25 (28.7)	49 (21.0)	1.52 (0.87–2.65)	0.15
Unit of hospitalization	87	233		
AC	58 (66.7)	184 (79)	1	
IC	10 (11.5)	19 (8.2)	2.01 (1.06–3.81)	0.03
LC	19 (21.8)	30 (12.9)	1.67 (0.74–3.77)	0.22
Nosocomial acquisition	87	233		
No	58 (66.7)	151 (64.8)	1	
Yes	29 (33.3)	82 (35.2)	1.08 (0.64–1.82)	0.76
Urinary catheter	87	232		
No	65 (74.7)	177 (76.3)	1	
Yes	22 (25.3)	55 (23.7)	1.09 (0.62–1.93)	0.77
Prior (1 yr) hospitalization	73	195		
No	29 (39.7)	100 (51.3)	1	
Yes	44 (60.3)	95 (48.7)	1.60 (0.93–2.76)	0.09
Prior (1 yr) UTI	73	195		
No	43 (58.9)	147 (75.4)	1	
Yes	30 (41.1)	48 (24.6)	2.14 (1.22–3.75)	0.008
Prior (1 yr) urinary catheter	72	189		
No	53 (73.6)	154 (81.5)	1	
Yes	19 (26.4)	35 (18.5)	1.26 (0.67–2.34)	0.48
Prior (6 mo) antibiotic exposure	87	233		
No	60 (69)	180 (77.3)	1	
Yes	27 (31.0)	53 (22.7)	1.53 (0.88–2.64)	0.13

[a] I-R, intermediate and resistant strains; S, susceptible strains.

population (sociodemographic, epidemiological, and clinical parameters), risk factors for infections caused by resistant microorganisms can be determined. In our literature search, concerning *E. coli*, we found only six studies, three of which were retrospective, that determined these risk factors (Table 8). Ciprofloxacin was the most frequently studied antibiotic. We evaluated risk factors for resistance to AMC, FQs (four antibiotics), and SXT in hospitalized patients with UTI caused by *E. coli*. In our logistic-regression model, a UTI during the previous year was the common risk factor for resistance to the different antibiotics studied. In two published studies which evaluated risk, one showed a significant association between antibiotic resistance and UTIs (10, 13). Although a prior UTI was probably associated with prior antibiotic exposure, the latter was significantly associated with resistance only to AMC in our multivariate analysis. Prior antibiotic treatment was analyzed in the six studies reviewed and was frequently associated with infection due to resistant *E. coli* (five of six univariate analyses). Similary, when prior quinolone use was evaluated, it was always a significant risk factor. Most (three of four) of these studies evaluated only ciprofloxacin-resistant *E. coli* strains, for which cross-resistance to all other FQs is a frequent occurrence (6). Therefore, our population of FQ-resistant strains was likely less multiresistant to FQs than those described in previous publications (13, 17, 31). In our logistic regression model, a prior urinary catheter was significantly associated with AMC resistance, in agreement with the work of De Mouy et al. (10). We found that patients >65 years old and men had higher risks of UTIs caused by FQ-resistant *E. coli* strains. These findings support those of Ena et al. (13) and Garau et al. (17).

TABLE 7. Multivariate analysis of independent risk factors for *E. coli* resistance to SXT

Risk factor	OR (95% CI)	*P* value
Sex		
Female	1	
Male	1.91 (1.01–3.60)	0.046
Unit of hospitalization		
AC	1	
IC	2.18 (0.91–5.21)	0.008
LC	1.26 (0.52–3.06)	0.6
Prior (1 yr) UTI		
No	1	
Yes	2.03 (1.08–3.80)	0.03

TABLE 8. Risk factors for infections caused by resistant *E. coli* strains

Characteristic of risk factor	Pena et al. (31)	Ena et al. (13)	Allen et al. (1)	Garau et al. (17)	Lepelletier et al. (27)	De Mouy et al. (10)
Country, period of study (type of study)	Spain, 1988–1992 (prospective)	Spain, 1990–1992 (retrospective)	Canada, 1992–1994 (retrospective)	Spain, 1992–1997 (retrospective)	France, 1996 (prospective)	France, 1998 (prospective)
Population	Hospitalized adults	Hospitalized NR[a]	Hospitalized and outpatient children	Hospitalized NR	Hospitalized NR	Outpatients, all ages
Antibiotic(s) studied	Ciprofloxacin	Ciprofloxacin	SXT	Ciprofloxacin	Panel[b]	Panel[c]
Infection studied	Bacteremia	UTI	UTI	Bacteremia	All isolates	UTI
Risk factors studied						
Age	Yes	Yes (>65 yr)[d,e]	Yes (2–6 yr)[d,e]	Yes (>65 yr)[d]	Yes	Yes
Sex	Yes	Yes (men)[d]	Yes	Yes (men with UTI)[d]	Yes	Yes
Chronic underlying disease	Yes[d]	Yes[d]	Yes[d]	Yes[d]	Yes	No
Genitourinary tract disorder	No	Yes[d,e]	Yes[d,e]	No	No	No
Nosocomial acquisition	Yes	Yes	No	Yes	Yes	
Unit of hospitalization	No	Yes[f]	No	No	Yes	
Source of infection	Yes (tract urinary)[d]			Yes (origin unknown)[d]	Yes	
Complicated UTI	No	Yes[d]	Yes	Yes[d]	No	No
Urinary catheter	Yes	Yes[g,e]	No	Yes[d,e]	Yes	Yes[h]
Immunosuppressive drugs	Yes	No	No	No	Yes[d,i]	No
Prior hospitalization	No	No	Yes (<1 yr)[d,e]	No	No	Yes (≤6 mo)[j]
Prior UTI	No	Yes (duration NR)	No	No	No	Yes (≤6 mo)[k]
Prior urinary catheter	No	No	No	No	No	Yes (≤7 days)[h]
Prior surgery[h]	Yes (≤1 mo)[d]	Yes (≤1 mo)	No	Yes (duration NR)	Yes (≤1 mo)	No
Prior antibiotic use	Yes (≤6 mo)[g]	Yes (≤1 mo)	Yes (≤6 mo)[d, e]	Yes (≤3 mo)[d,e]	Yes (≤1 mo)[i]	Yes (≤6 mo)[k]
Prior quinolone use	Yes (≤6 mo)[d,e]	Yes (≤1 mo)[d,e]		Yes (≤3 mo)[d,e]	Yes (≤1 mo)[d]	No

[a] NR, not reported.
[b] Antibiotics tested were AMZ, AMX, ticarcillin, cephalothin, ceftazidime, nalidixic acid, ciprofloxacin, ofloxacin, norfloxacin, gentamicin, amikacin, tobramycin, nitrofurantoin, and SXT.
[c] Antibiotics tested were AMZ, AMC, nalidixic acid, ciprofloxacin, gentamicin, and SXT.
[d] Significant by univariate analysis.
[e] Significant by multivariate analysis.
[f] Univariate analysis indicates significant association of resistance with patient hospitalization in urology and other than general medicine units.
[g] Trend toward significance by univariate analysis.
[h] Risk factor significantly associated with resistance to AMZ and nalidixic acid by univariate analysis.
[i] Risk factor significantly associated with resistance to at least one antibiotic of the panel by univariate analysis.
[j] Risk factor significantly associated with resistance to all antibiotics tested except AMC by univariate analysis.
[k] Risk factor significantly associated with resistance to all antibiotics tested except gentamicin by univariate analysis.

The role of the unit of hospitalization has rarely been studied. According to our analysis, the unit of hospitalization appeared to be significantly associated with SXT resistance (IC unit), and there was a trend toward significance for AMC resistance (LC unit, multivariate analysis). Nosocomial acquisition was not found to be a risk factor for resistance in our study or in the six other studies. In a comparative study of nosocomial and community-acquired bacteremias due to *E. coli*, Olesen et al. (30) did not find major differences between the two origins. However, according to Perrin et al. (33), who studied elderly patients hospitalized in a geriatric hospital, the rates of resistance to AMC, floxacin, and SXT for *E. coli* strains responsible for nosocomial UTIs were higher than those for strains responsible for community-acquired UTIs.

Comparisons among these different published studies are difficult. They should take into account the fact that they were carried out at different periods. For a recent class of antibiotics, e.g., FQs for our study, the time lapse between their commercialization and the study period varied, and, consequently, the time of population exposure to these drugs varied. These studies frequently concerned a targeted population with defined sociodemographic, epidemiological, and clinical parameters, and the infection site also varied according to the study (UTI, bacteremia, all isolates). For example, the definition of a given risk factor was not the same in all the studies; e.g., the time lapse between prior exposure to an antibiotic and the episode studied could range from 1 to 6 months. Moreover, the comparison must consider the definition of resistance to antibiotics (MIC breakpoint), which can vary by country and when the study was conducted.

Our results indicate that nosocomial UTIs did not seem to be a risk factor for *E. coli* resistance, in accordance with the results of other studies. We found that prior antibiotic exposure was significantly associated with resistance only to AMC. A previous study showed that this risk factor is also associated with resistance to other antibiotics, particularly FQs and SXT. However, the period of exposure was variable and was frequently <6 months. Moreover, we think that other parameters

such as posology, the duration of the prior antibiotic treatment, and the exact interval between the prior antibiotic treatment and the occurrence of UTI probably had a role, but it is not easy to record these parameters. That may explain why nobody, to our knowledge, has studied these parameters. Only two of six previous studies evaluated prior UTI as a risk factor. We observed that the presence of this risk factor during the previous year was constantly associated with *E. coli* resistance to the different antibiotics studied. That is the reason why physicians treating patients with UTIs must look for this risk factor, particularly in ambulatory patients, to forecast the higher risk of failure of an empirical antimicrobial treatment.

We found very few publications that addressed the subject of the study described in this report, probably because such an undertaking requires the collection of numerous data which are particularly difficult to obtain when the study is retrospective. Careful interpretation of these analyses of the risk factors associated with infections due to resistant strains according to the population, infection site, and period studied should contribute to the formulation of a better approach to the problem of antibiotic resistance and provide a means of making a rational choice of empirical antibiotic therapy to try to limit the evolution of resistance.

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